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Pulmonary diffusing capacity in chronic dialysis patients

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Abstract Patients with end-stage renal disease treated by hemodialysis with bioincompatible membranes are exposed during the dialysis period to acute effects on lung microcirculation, which may result in pulmonary fibrosis and diffusion defects in long-standing dialysis. To investigate the occurrence of these possible chronic pulmonary alterations, we determined lung function in patients with chronic renal failure not undergoing hemodialysis and in patients who had been receiving regular hemodialysis both for short and long periods of time. Forty-three patients divided into three groups were studied: 17 patients before dialysis with a mean (SD) creatinine clearance of 14.1 (6.8) ml/min/1.73 m^2, 10 patients receiving regular hemodialysis for a period of less than 12 months (mean 6.4 $\pm$ 3.5 months), and 16 patients receiving regular hemodialysis for more than 5 years (mean 8.3 $\pm$ 3.6 years). First-use bioincompatible cellulosic dialysis membranes were used in all the cases. The following parameters were recorded: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), residual volume (RV), carbon monoxide transfer factor (T_{LCO}), accesible lung volume (V_A), carbon monoxide transfer factor/accesible lung volume (K_{CO} — that is, T_{LCO}/V_A), and arterial blood gases. Patients receiving regular hemodialysis for more than 5 years showed significantly lower values of T_{LCO} and K_{CO} than patients before dialysis and patients receiving regular hemodialysis for less than 12 months. Seventy-five percent of patients on long-term hemodialysis had markedly reduced T_{LCO} or K_{CO} values (below 80% of the reference value) as compared with 17% of patients before dialysis and 10% of patients dialyzed for less than 12 months ($P < 0.001$). Differences among groups for the remaining parameters were not observed. In conclusion, patients undergoing long-term regular hemodialysis with a bioincompatible membrane showed a selective reduction in pulmonary diffusing capacity possibly due to chronic pulmonary fibrosis. © 2002 Elsevier Science Ltd. All rights reserved.

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Keywords end-stage renal disease; hemodialysis; bioincompatible membranes; pulmonary diffusing capacity; pulmonary fibrosis.

INTRODUCTION

Patients with end-stage renal disease treated by hemodialysis are exposed to continuous pulmonary insults of multifactorial origin (1). Fluid retention predisposes to pulmonary edema, which occurs more frequently in the presence of concomitant heart disease (2). Moreover, pulmonary calcification in chronic dialysis patients has been associated with fibrotic changes and pulmonary dysfunction (3,4). On the other hand, membrane bioincompatibility results in the activation of the complement cascade and simultaneous changes in receptors of cell adhesion molecules within the pulmonary vasculature, which in turn leads to pulmonary vascular leukostasis (5) and significant pulmonary hypertension (6). Pulmonary vascular leukostasis and pulmonary hypertension have been implicated in the pathogenesis of hypoxemia during the hemodialysis session (7,8). Changes in lung function induced by hemodialysis using a bioincompatible membrane have been assessed during the short dialysis period, but whether these acute effects on lung microcirculation have any long-term significance with regard to possible induction of pulmonary fibrosis and impairment of pulmonary diffusing capacity have been scarcerly investigated.

Taking into account that an analysis of pulmonary diffusing capacity is a reliable non-invasive method for the study of pulmonary interstitium, a study was designed to assess the possible development of pulmonary fibrotic changes in patients undergoing long-term hemodialysis

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with a bioincompatible membrane. To this purpose, carbon monoxide transfer factors, spirometric and plethysmographic parameters were measured in patients with end-stage renal disease receiving hemodialysis with a bioincompatible membrane for a prolonged period of time and compared with patients in predialysis situation and with patients dialyzed for a short period.

METHODS

Patients

A total of 43 patients with chronic renal failure participated in a cross-sectional study. Patients were divided into three groups as follows: patients in group 1 (n=17) had chronic renal failure with creatinine clearance <25 ml/min/1.73 m^2 (mean 14.1 $\pm$6.8 ml/min/1.73 m^2) and were followed at regular intervals at the outpatient nephrology clinic of our hospital; patients in group 2 (n=10) had been receiving regular hemodialysis for a period between 3 and 12 months (mean 6.4$\pm$3.5 months); and patients in group 3 (n=16) had been receiving regular hemodialysis for a period of at least 5 years (mean 8.3$\pm$3.6 years). Each patient was informed and they agreed to participate in the study. The study protocol was approved by the Institutional Review Board.

Demographic characteristics of patients and etiology of renal failure are shown in Table 1. In the two groups of patients on chronic hemodialysis treatment, frequency of dialysis was three times a week. All the patients were dialyzed using bicarbonate-based dialysis fluid. Non-reused bioincompatible cellulosic hemodialysis membranes were employed in all the cases. Patients in group 2 were dialyzed using either cuprophane (n=5) or rayon-cuproammonium (n=5) membranes. Patients in group 3 were dialyzed using cuprophane (n=6), cellulose acetate (n=5), or rayon-cuproammonium (n=5) membranes. Patients suffering from atrial dysrhythmia, moderate or severe heart disease with systolic dysfunction (fractional shortening $\leq$50% on echocardiography), chronic lung disease, or treated with drugs that can damage the lungs were excluded. Current smokers and ex-smokers were also excluded. All patients had been in stable clinical condition for at least 3 months preceding the study. None had any clinical evidence of heart failure at the time of the study. Moreover, none of the patients in groups 2 and 3 had had any recent problem with the vascular access for hemodialysis or had catheters inserted temporarily or permanently for that purpose.

Baseline M-mode echocardiography was performed in all the patients. Hematocrit values and serum hemoglobin concentrations were determined before dialysis. In all the patients undergoing on hemodialysis treatment, urea reduction ratio (URR) was the mean value for last two measurements in the preceding months, and the residual creatinine clearance (C_{cr}), the value obtained in the last control. Serum calcium and phosphorus concentrations were the mean of three measurements and serum intact parathyroid hormone (iPTH) was the mean of two measurements performed within 6 months of starting the study. Patients in groups 2 and 3 were studied between 12 and 18 h after the end of hemodialysis session.

Study design

On the day of the study an arterial blood sample was taken for blood gas analyses. A forced spirometry was carried out using a Masterlab model 3.14 spirometer (Masterlab, Jaeger, Würzburg, Germany). Alveolar gas exchange was measured by the carbon monoxide single-breath test and respiratory mechanics with the Masterlab whole body plethysmograph. The following parameters were recorded: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), residual volume (RV), carbon monoxide transfer factor (T_{LCO}), accessible lung volume (V_A), and carbon monoxide transfer factor/accesible lung volume (K_{CO}—that is, T_{LCO}/V_A). At least three reproducible tests

Table 1. Details of patients studied

	Group 1 n = 17	Group 2 n = 10	Group 3 n = 16
Age, years, mean (SD)	63 (14)	60 (18)	61 (10)
Sex (M/F)	8/9	5/5	4/12
Diagnoses			
Glomerulonephritis	4	1	3
Interstitial nephropathy	5	4	4
Diabetes mellitus	2	0	1
Nephroangiosclerosis	1	2	0
Chronic saturnism	1	0	0
Adult polycystic kidneys	2	3	4
Unknown	2	0	3

were carried out for each measurement and the best was recorded. Comparisons were made with the normal ranges from Cotes (9) except for K_{CO}, which is also expressed as the absolute value. Measured parameters were within the normal range when values recorded were $>80\%$ of the corresponding reference data.

Statistical analysis

Between-group differences were assessed with the Student's *t*-test and the analysis of variance (ANOVA) for data with normal distribution and with the Mann–Whitney *U*-test for data with distributions departing from normality. Relationships between continuous variables were assessed with the Pearson product-moment correlation coefficient (r). Statistical significance was set at $P<0.05$. All the values are expressed as means (SD).

RESULTS

Hemoglobin and hematocrit values were similar in all the groups (Table 2). Thirty-five percent of patients in group 1, 60% in group 2, and 50% in group 3 received treatment with recombinant human erythropoietin. Mean ($\pm$SD) duration of dialysis sessions was similar among patients in group 2 (226 ± 14 min) and group 3 (232 ± 18 min). There were no differences in URR either (group 2, $72.4\pm2.1\%$ *vs* group 3, $74.7\pm3.4\%$). However, as expected, C_{cr} was significantly higher in patients in group 2 (1.32 ± 0.79 ml/min/1.73 m^2) than in patients in group 3 (0.19 ± 0.21 ml/min/1.73 m^2) ($P<0.01$). Serum phosphorus concentrations, Ca $\times$ P product, and iPTH levels were significantly higher in patients in 3 as compared with patients in either group 1 or 2 (Table 2). Thirty percent of patients in group 1, 40% of those in group 2, and 48% of those in group 3 fulfilled the criteria of left ventricular hypertrophy on echocardiography.

As shown in Table 2, PaO_2 and $PaCO_2$ levels were similar in all the groups. Although bicarbonate and pH values were significantly lower for patients in group 1 than for those in the remaining groups, differences of these parameters between patients in groups 2 and 3 were not observed. On the other hand, differences among groups for FVC, FEV_1, TLC, or RV were not detected but T_{LCO} and K_{CO} values were significantly lower in patients in group 3 than in the remaining groups (Table 2). Absolute K_{CO} values were also significantly reduced in group 3 as compared with groups 1 and 2 (Fig. 1). In group 3 patients, however, no correlation between decreases in T_{LCO} or K_{CO} and serum concentrations of iPTH or Ca $\times$ P product values was observed. On the other hand, T_{LCO} and K_{CO} values were not significantly different in patients in this group when those with or without left ventricular hypertrophy were compared. Seventy-five percent of patients in group 3 had low T_{LCO} or K_{CO} values ($<80\%$ predicted) as compared with 17% of patients in group 1 and 10% of patients in group 2 (Table 3). In relation to spirometric patterns, 10 (62.5%) patients in group 3 had abnormal K_{CO} with no changes in other lung function parameters.

Table 2. Analytical parameters and results of blood gas analyses and pulmonary function tests

Data	Group 1 $n=17$	Group 2 $n=10$	Group 3 $n=16$
Hemoglobin (g/dl)	11.1 (1.0)	10.8 (0.7)	10.7 (1.4)
Hematocrit (%)	32.8 (3.3)	31.8 (2.3)	32.5 (2.4)
Calcium (mg/dl)	9.3 (0.3)	9.4 (0.5)	9.8 (0.8)
Phosphorus (mg/dl)	4.8 (0.9)*	4.4 (1.0)**	5.7 (1.0)
Ca $\times$ P product	44.7 (8.8)*	41.7 (11.4)**	52.6 (11.4)
iPTH (pg/ml)	136.0 (74)***	198.0 (62)**	387.0 (293)
PaO_2 (mmHg)	82.1 (9.9)	79.4 (6.9)	78.3 (10.5)
$PaCO_2$ (mmHg)	36.3 (3.3)	38.1 (8.6)	42.0 (9.6)
Bicarbonate (mmol/l)	22.7 (3.0)*,[a]	25.9 (2.9)	26.2 (2.0)
pH	7.39 (0.04)*,[a]	7.41 (0.05)	7.42 (0.04)
FVC (% predicted)	93.8 (10.6)	94.8 (19.0)	99.4 (14.4)
FEV_1 (% predicted)	92.7 (13.8)	96.7 (17.3)	96.5 (17.3)
TLC (% predicted)	92.0 (10.2)	96.3 (12.1)	93.6 (12.7)
RV(% predicted)	104.3 (17.6)	117.1 (22.8)	111.2 (20.8)
T_{LCO} (% predicted)	106.6 (13.1)**	110.1 (13.9)***	86.2 (14.0)
K_{CO} (% predicted)	104.0 (25.2)*	108.1 (23.0)***	76.0 (12.2)

Values are means (SD).
*$P<0.05$, **$P<0.01$, and ***$P<0.001$ *vs* group 3.
[a]$P<0.05$ *vs* groups 2 and 3.

DISCUSSION

This study provides an evidence of pulmonary diffusing capacity abnormalities in patients with end-stage renal disease receiving regular hemodialysis for many years. In most cases, derangement of diffusing capacity was not associated with changes in respiratory mechanics indicating that some form of selective damage in the alveolo-capillary wall that interferes with alveolar gas exchange had occurred. The low incidence of these abnormalities in patients with long-standing severe kidney disease not treated with hemodialysis as well as in patients enrolled on dialysis programs for a short period of time ($<$ 12 months) suggests that the pathogenetic factor(s) involved in diffusing capacity derangements are associated with long-term dialysis treatment.

Parameters of pulmonary diffusing capacity in patients with chronic renal failure on hemodialysis programs have been determined in a number of studies with controversial results. In the study of Bush and Gabriel (10), 70% of patients with varying degrees of chronic renal failure not undergoing dialysis and a similar proportion of those in the hemodialysis program for a mean of 2.1 years had evidence of pulmonary diffusing capacity abnormalities as defined by reductions in T_{LCO} and K_{CO}. It should be noted, however, that a large proportion of patients in this study were current smokers or ex-smokers, and most of them (90%) had associated spirometric abnormalities. Similar results were found by others (11). Kao *et al*. (12) reported a decrease in alveolar permeability using ^{99m}Tc-diethylene triamine pentaacetate (DTPA) radioaerosol inhalation during lung scintigraphy in 24 patients on hemodialysis, which was not correlated with the length of time of dialysis treatment. By contrast, Yenicerioglu *et al*. (13) also using ^{99m}Tc-DTPA lung scintigraphy, did not observe abnormalities of alveolar permeability in 20 hemodialysis patients either before or after dialysis sessions. In another study, Dujic *et al*. (14) found a reduction of T_{LCO} in 25 patients receiving hemodialysis, which was related to anemia given that T_{LCO} decrease reversed with blood transfusion. Chan *et al*. (15) in patients with chronic renal failure on hemodialysis, reported T_{LCO} and RV values in the high normal range of a predicted value (115.7 and 157.8%, respectively) that showed a trend towards normalization at 6 months of renal transplantation. These authors attributed high T_{LCO} and RV values to the chronic vascular congestive pulmonary state during the dialysis period, which would improve following renal transplantation. It is possible that all these apparently contradictory results may be explained by different criteria of patient selection, methodologies, characteristics of dialysis procedure, and time on dialysis. In our study, in which the groups of patients were comparable with respect to selection criteria, degree of anemia, and characteristics of the hemodialysis session, two markedly different situations were encountered. On the one hand, patients receiving hemodialysis for a short period of time showed T_{LCO} and RV values in the upper range of nor-

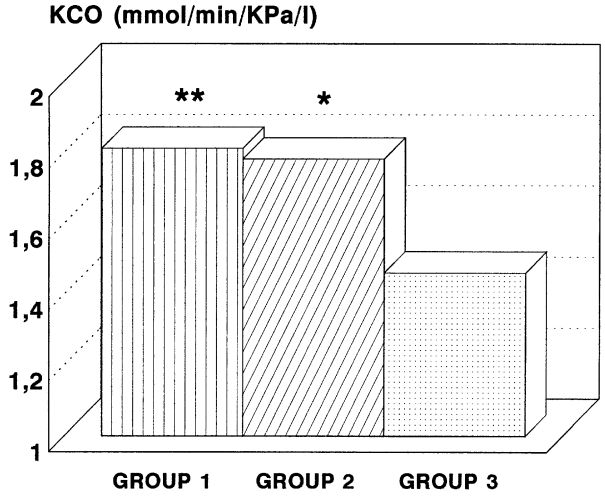

Fig 1. Absolute values of K_{CO} in the three groups of patients (*$P < 0.05$ and **$P < 0.01$ *vs* group 3).

Table 3. Numbers of patients in each group with particular abnormalities of lung function

Data	Group 1 n = 17 (%)	Group 2 n = 10 (%)	Group 3 n = 16 (%)
Abnormal FEV_1 or FVC	2 (11.7)	2 (20)	3 (18.7)
Abnormal TLC or RV	2 (11.7)	1 (10)	2 (12.5)
Abnormal T_{LCO} or K_{CO}	3 (17.7)**	1 (10)**	12 (75)
Normal pattern	14 (82.3)	8 (80)	13 (81.2)
Obstructive pattern	2 (11.7)	0	2 (12.5)
Restrictive pattern	1 (5.8)	1 (10)	1 (6.2)
Mixed	0	1 (10)	0
K_{CO} only abnormal	2 (11.7)**	1 (10)**	10 (62.5)

**$P < 0.01$ *vs* group 3.

mality, which is in agreement with findings reported by Chan *et al*. (15). However, 75% of patients receiving hemodialysis for a long period of time had decreased T_{LCO} and K_{CO} values, most of which showed isolated pulmonary diffusing capacity alterations, that is, in the absence of associated spirometric abnormalities. This suggests the presence of diffuse interstitial pulmonary disease.

The cause of pulmonary fibrotic changes in patients on hemodialysis programs may have a multifactorial origin. In the present study, patients with moderate or severe heart disease that may be potential causes of pulmonary edema, interstitial lesions, and pulmonary diffusing capacity derangement were excluded. All the patients were dialyzed using bicarbonate-based dialysis fluid, so that the effect of acetate on cardiovascular hemodynamics, pulmonary hemodynamics, and lung function during the dialysis session was excluded (16,17).

Calcification of the lungs has attracted considerable clinical attention and this phenomenon has been implicated in the pathogenesis of respiratory impairment in patients with kidney disease. Different studies have detected a high prevalence of lung calcifications in patients with kidney disease on dialysis when ^{99m}Tc-diphosphonate scans are performed, while calcifications are rarely seen on plain radiographs (18–20). The pathogenesis of these calcifications has not been clearly elucidated, although they are thought to have a multifactorial origin. Secondary hyperparathyroidism is one of the main mechanisms leading to soft tissue calcification in patients with end-stage renal disease. However, most studies have failed in finding a relationship between pulmonary calcification and serum iPTH concentrations or Ca x P product (3,18,19). In the study of Jarava *et al*. (20), patients with pulmonary calcifications detected by ^{99m}Tc-diphosphonate scanning were older and showed higher levels of PTH than patients with negative scans. In our study, ages of patients in the three groups were similar. Patients who had been on hemodialysis for more than 5 years had significantly higher Ca x P product and serum iPTH levels than patients in the remaining two groups but the lack of correlation between Ca x P product and/or PTH levels and reductions in T_{LCO} or K_{CO} does not allow to establish any definite conclusions.

The effect of bioincompatible membranes that had been used in patients receiving dialysis for many years on pulmonary function abnormalities and, in particular, on derangement of pulmonary diffusing capacity, is another factor that should be taken into consideration. In the course of hemodialysis with bioincompatible membranes, complement-mediated activation of granulocytes and increased expression of adhesion-promoting molecules, such as Mac-1 (CD11b-CD18) (21–24), CD13 (25), and CD45 (24) has been recognized. We have recently shown that the interaction of C5a with the CD88 cell receptor is involved in the membrane-dependent granulocyte and monocyte activation (26). Increase in adhesion molecule receptors expression specially Mac-1 has been implicated in the pathogenesis of leukopenia and marked increase in adhesion of granulocytes to the endothelium, leading to pulmonary leukosequestration (22,23,25). In recent years, evidence has accumulated that other neutrophil effector functions, such as reactive oxygen intermediate production play an important role as well (27). In addition to leukostasis with the release of mediators causing inflammation in the pulmonary microcirculation, other hemodynamic changes consisting in pulmonary hypertension secondary to vasoconstriction occur (6). It has been reported that pulmonary vasoconstriction is mediated by thromboxane A_2 from the lung and other tissues due to stimulation by complement cascade-derived products (28). Theoretically, it may be postulated that the development of pulmonary hypertension in each dialysis session using a bioincompatible membrane accompanied by an inflammatory reaction at the microcirculation level, may cause chronic lesions in the alveolo-capillary wall, with collagen deposition resulting in diffuse interstitial pulmonary disease and impairment of diffusing capacity, which may have occurred in our patients maintained on hemodialysis for a long period of time.

We conclude that in patients maintained on hemodialysis for a long time, there is a selective impairment in pulmonary diffusing capacity. It seems that membrane bioincompatibility may be an important cause of diffusing capacity derangement, although the effect of other factors cannot be excluded. Further prospective, controlled trials where, as many as possible, a large number of factors which might affect lung function are kept comparable are needed to prove the superiority of biocompatible over bioincompatible dialysis membranes.

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